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Penicillamine at 21: Its Place in Therapeutics Now

Session I

Chairman Professor R A McCance

Brief Observations on the Management of Wilson's Disease

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Wilson's disease results from a genetically determined metabolic deviation which leads to accumulation of copper in the liver, kidneys and brain. The primary defect has not been determined with certainty, but may result from a lysosomal malfunction (Sternlieb *et al.* 1973) with failure to excrete copper via the bile.

Treatment requires the removal of the excess copper and thereafter the maintenance of copper balance so that the metal does not reaccumulate in the tissues. Patients so treated can live for many years, perhaps three score years and ten, in normal health and lead a full and active life. Such treatment requires 'a supreme capacity for taking trouble'; there is no place for the philosophy of giving some penicillamine and seeing what will happen.

Before treatment can be started it is essential that the diagnosis be established beyond all possible doubt, not only in symptomatic patients but also in their presymptomatic relatives who have the biochemical lesion but who have not as yet developed signs of the disease; in this there is no possible margin of error. The diagnosis must rest on history, physical findings and demonstration of the typical abnormality in copper transport. These procedures have been described in detail elsewhere (Walshe 1975).

Before beginning treatment it is necessary to know, in addition to values for serum copper and cæruloplasmin, urine copper levels, both basal and after a test dose of penicillamine, the blood count and renal function, as these are often abnormal before treatment is started and the abnormality, if not already documented, may be wrongly attributed to a toxic action of the drug. It must also be remembered that treatment will have to be continued for many years (most well-managed patients will outlive their doctors), and if the necessary data are not established initially, all sorts of difficulties may well be encountered, unnecessarily, at a later date.

The most active of the medical chelating agents at present available for mobilizing copper is penicillamine (dimethyl cysteine), and this has the additional advantage over the others (BAL and EDTA) that it is active when given by mouth, a major consideration when a drug has to be given for a lifetime. The size of the dose varies with the age and size of the patient and also with the severity of the illness. An average starting dose for an adult is 500 mg three times a day before meals. The timing is important as it has been shown previously (Walshe 1967) that penicillamine will promote a very much greater

excretion of radiocopper if the drug is given before rather than after the radioisotope.

For very severely ill patients it may seem desirable to start with as much as 1 g three times a day; such a dose can be given for up to three months, after which it should be reduced to not more than 2 g daily. Presymptomatic or early symptomatic patients can be controlled with a smaller dose as can children, but it is seldom wise to give less than 500 mg daily, even to quite young patients. It has not been my experience that it is necessary to start with a very small dose and increase this only very gradually; patients with Wilson's disease tolerate penicillamine very much better than do patients with rheumatoid arthritis.

Some patients show a further deterioration in their neurological lesion after starting treatment, and while this must always cause concern it is no reason for stopping therapy. The great majority eventually make a good symptomatic recovery, though the time taken for this to happen may be anything from three months to two years. Patients with hepatic Wilson's disease also respond well to treatment provided that severe portal hypertension and fluid retention have not already developed, for in such patients the prognosis must be guarded. Once a good clinical remission has been established together with a corresponding reduction in blood and urine copper levels, the penicillamine dose may be reduced for maintenance purposes, though this should seldom be less than 1 g daily. In such patients, if the dose is not adequate, biochemical relapse always precedes clinical relapse, so that regular biochemical monitoring will permit the penicillamine dose to be raised, if necessary, before any clinical damage occurs. In women taking oral contraceptives there may be a rise in serum copper and cæruloplasmin without a corresponding rise in urinary copper. In such patients a change in dose is not necessary. A very few patients with what can only be described as an akinetic type of Wilson's disease do not seem to respond to any form of chelation treatment, and have a progressive and fatal neurological lesion. I have seen 4 such patients.

Besides being a weak pyridoxine antimetabolite (Jaffe *et al.* 1964) which may lead, under specific conditions, to pyridoxine depletion (Gibbs & Walshe 1966), penicillamine can give rise to a wide variety of toxic reactions. In patients with Wilson's disease these are not as common as in patients with rheumatoid arthritis and generally not as severe, but they do occur and involve principally the bone marrow and renal function. I have found it necessary to withdraw penicillamine in 10 patients, 5 males and 5 females. In the male patients the reason was the development of the nephrotic syndrome in 3, rash, fever and hæmaturia in one, and a Stevens–Johnson-like syndrome in one. In the female patients five different lesions necessitated penicillamine withdrawal: thrombocytopenia, leukopenia, excess collagen fragility, rheumatoid-like arthritis with positive antinuclear factor, and hæmolytic anæmia. Four other patients have complained of arthritic symptoms and have had positive antinuclear factor, a positive Rose–Waaler test or a positive LE cell preparation on occasion; all have been managed on a reduced penicillamine dose, as was one male patient who showed severe weight loss, vasculitis and a very high ESR. One female patient has also been seen with agammaglobulinæmia. Unfortunately her serum proteins before treatment were not characterized so that the relationship of this finding to therapy is not clear, thus illustrating the importance of a full laboratory work-up before giving penicillamine.

Penicillamine cannot be withdrawn from a patient with Wilson's disease without facing the consequence of an eventual death from this illness, unless some alternative treatment is instituted. It has been shown that a satisfactory alternative is trien 2HCl (triethylene tetramine 2HCl) (Walshe 1969, Dixon, Gibbs & Walshe 1972, Walshe 1973), and all 10 patients mentioned above have been managed with this new drug. Eight were largely free of signs at the time of change of therapy, but 2 were in the early severely symptomatic stage of the illness. In both the remission has been very satisfactory. Unfortunately, trien 2HCl is not available on the market as a therapeutic compound, and neither the conscience of the community nor the pharmaceutical industry, handicapped as it is by the Medicines Act, has been sufficiently touched to force the manufacture of this drug, which is still produced for those patients needing it in my laboratory. This is surely a state of affairs which is as unsatisfactory as it must be temporary. The future of these patients, when I retire, remains extremely problematical.

In summary, it can be said that the diagnosis of Wilson's disease must be established beyond doubt before treatment is started and that a full biochemical work-up is essential. Penicillamine is the drug of choice and should be given in doses of 1.5–2 g daily until clinical remission has been established, after which a smaller maintenance dose is usually sufficient; a pyridoxine supplement is necessary only during growth,

pregnancy and intercurrent infection. About 10% of patients develop toxic symptoms and for these change to the alternative chelating agent trien 2HCl is essential, but this must be produced in a laboratory since it is not commercially available.

The best management of Wilson's disease requires much experience and endless attention to detail. There is no case for a trial and error type of management.

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DISCUSSION

Dr Sumner (*Leeds*): Does Dr Walshe have any autopsy material from recovered Wilson's disease patients who have been treated?

Dr Walshe: Yes, from two treated patients who died, both of them men about 50 years old. One had what was called a coronary thrombosis, being found dead in his bed in the morning. We do not really know what happened to him. The other man – in his late 40s – had what was called a lipid pneumonia, which I thought a rather odd illness, and he died rapidly. Having been taken seriously ill overnight, he was dead on arrival at the Radcliffe Infirmary. Copper determinations on his brain and liver were in the normal range.

Dr I A Jaffe (*New York*): In connexion with the point about nephropathy in the male sex, rheumatologists see a fair amount of it in females.

Dr B Sarkar (*Toronto*): Dr Walshe mentioned that there is a low serum copper level with penicillamine and a high one with triethylene tetramine. Was urinary copper excretion comparable?

Dr Walshe: More copper can be removed by triethylene tetramine from an untreated patient who is saturated with copper. But, in the late stages, when patients have been on penicillamine for a long time, penicillamine is more effective in removing further copper. But, by then, the blood copper level is so low that it is not influenced by a single test dose.

Dr H Lehmann (*Cambridge*): Dr Walshe said that he wants to find the blood count before treating a patient. Does it influence treatment? What is the point of observing the blood count if there is no choice?

Dr Walshe: Many patients with Wilson's disease start with a very disturbed blood count, in particular those with liver damage and splenomegaly, who will have about 20 000 or 30 000 platelets and perhaps 1500 to 2000 white cells per c.mm. If this is not known before treatment is started, and a blood count is done a month later, it might be thought these patients had been poisoned with penicillamine when this, in fact, is probably not the case. Of course, treatment has to stop if we do find they are being poisoned by penicillamine, and be changed to triethylene tetramine. In the rheumatoid patients, if this happens, treatment is simply stopped.